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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/731,672 | 12/09/2003 | Shulamit Levenberg | 0492611-0530/MIT-10077 | 6356 |

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| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALINE K | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 06/03/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/731,672 | LEVENBERG ET AL. | |
| | Examiner | Art Unit | |
| | MAGDALENE SGAGIAS | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,59-71,73 and 75-79* is/are pending in the application.

4a) Of the above claim(s) *59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,71,73 and 75-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicant's arguments filed 02/28/2011 have been fully considered.

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 59-71, 73, 75-79 are pending. The amendment dated 02/28/2011 has been entered. Claims 6, 12, 20-21, 26, 35, 45-46, 51-58, 72 and 74 are canceled. Claims 59-70, are withdrawn. Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71, 73 and 75-79 are under consideration.

The declaration under 37 CFR & 1.131 of Shulamit Levenberg dated 02/28/2011 has been considered and is persuasive.

This rejection is **non-final.**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18, 41 contain the trademark/trade name MATRIGEL™ line 2. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade

name is used to identify/describe MATRIGEL™ and, accordingly, the identification/description is indefinite.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims **1-5, 7-11, 13-15, 17-19, 22-25, 27-34, 36-44, 48-49, 71 and 75-79** under 35 U.S.C. 103(a) as being unpatentable over **Sherwood et al** [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002)] in view of **Buttery et al** [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; **Athanasiou et al** [Arthroscopy, 14(7): 726-737, 1998] is withdrawn in view of the declaration under 37 CFR & 1.131 of Shulamit Levenberg dated 02/28/2011, which establishes that the instant invention was made prior to February 8, 2002, and therefore predates the effective filing date of the Sherwood reference (see p. 12 of the Response, filed 2/28/11).

The rejection of Claims **1, 16** under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of **Athanasiou et al,** (39th Annual Meeting, Orthopaedic Research Society, February 15-18, 1993, p 288) thereafter referred as **Athanasiou 2**) ] is withdrawn in view of the declaration under 37 CFR & 1.131 of Shulamit Levenberg dated 02/28/2011.

The rejection of Claims **1, 22, 39, 48** under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of **Bradham et al** (Matrix Biol, 14(7): 561-71, 1995) ] is withdrawn in view of the declaration under 37 CFR & 1.131 of Shulamit Levenberg dated 02/28/2011.

The rejection of Claims **1, 23, 47** under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of Bradham et al (Matrix Biol, 14(7): 561-71, 1995); **Kaushall et al, (**Nat. Med, 7: 1035-1040, 2001) ] is withdrawn in view of the declaration under 37 CFR & 1.131 of Shulamit Levenberg dated 02/28/2011.

The rejection of Claims **1, 23, 71, 43, 50, 73** under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002, IDS)] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of **Benvenisty et al, [**US 2002/0146678 (IDS)]; **Kojima et al** (Experimental Cell Research, 206: 152-156, 1993 (IDS) ] is withdrawn in view of the declaration under 37 CFR & 1.131 of Shulamit Levenberg dated 02/28/2011.

***New Claim Rejections - 35 USC § 103***

Claims **1-11, 13-15, 22-25, 27-34, 36-39, 44-49, 71, 73, 75-79** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Borenstein et al** (US 7371400 B2, filed January 2, 2002, claiming priority to Jan 2, 2001) in view of **Xu** (US 7,425,448, filed July 12, 2002; claiming priority to Jul 12, 2001).

Regarding claims **1, 23,** Borenstein et al teaches a tissue engineering construct, comprising a) embryonic or fetal cells, or stem cells, or genetically engineered cells (column 23, lines 3-11); b) a polymer scaffold consisting of a biocompatible, biodegradable, porous material (column 35, claim 27); c) a cell adhesion promoter, by teaching cells can be seeded onto the scaffold that are enriched for extracellular matrix molecules or peptides that enhance cell adhesion (column 22, lines 1-5), wherein zones of animal cell support comprise cell adhesion molecules (column 34, claim 21); and d) growth factors such as bone morphogenic proteins (BMP), epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I and II), TGF-.beta that enhance cellular or tissue ingrowth (column 21, lines 52-60).

Regarding claims **4, and 15** Borenstein et al teach microfabrication and biodegradable polymer scaffolds and microfluidics for tissue engineering comprising poly(lactic-co-glycolic acid) (PLGA) (column 32, example 4) and suggest particularly useful are Poly-L-lactic acid (PLLA) and poly-glycolic acid (PGA) because exhibit a high degree of crystallinity and degrade relatively slowly (column 8, lines 55-65).

Regarding claims **13, 36,** Borenstein et al teach cell adhesion can be mediated fibronectin of intergins (column 20, under cell adhesion to templates).

Regarding claims **14, 37,** Borenstein et al teach a polymer scaffold consisting of a biocompatible, biodegradable, porous material (column 35, claim 27).

Regarding claims **15, 38,** Borenstein et al teach tissue engineering construct, wherein the polymer of the cell support matrix is poly(D,L-lactide-co-glycolide (polylactide-co-glycolide)that is biocompatible and biodegradable (column 9, lines 1-14).

Regarding claim **16,** Borenstein teaches another polymer system can involve the use of RGD (Arg-Gly-Asp) peptides and the RGD sequence is part of the domain within the fibronectin

molecule that endows it with the ability to interact with the cell surface of fibroblasts, wherein the function of the fibronectin molecule is localized primarily to the RGD sequence, one of skill in the art can synthesize RGD peptides that allows differential cell adhesion in only selected areas and not others (column 10, lines 66-67, column 13, lines 1-16). Regarding claims **17-18,** Borenstein teaches cell attachment and lifting from scaffolds tested as possible substrates for the culture and lifting of endothelial cells and hepatocytes cultured on wafers coated with vitrogen Matrigel™ (1%), or gelatin (10 mg/ml) (column 28, lines 42-60) and fabrication of the molds begins by selection of an appropriate substrate for the micromachining process, wherein the choice of a substrate material for the mold is guided by many considerations, including the surface properties of the wafer, and the interaction of the wafers with the various cell types, extracellular matrix molecules ("ECM"), (column 6, lines 1-11) it would allow one of skill in the art to culture cells within the matrigel branched networks of the polymer and or other cell types on the top and bottom outer polymer surfaces.

Regarding claims **39, 71,** Borenstein et al teach tissue engineering construct, wherein the growth factor comprises insulin growth factor (IGF) (column 21. lines 55-60).

Regarding claim **75,** Borenstein et al teach tissue engineering construct, wherein the polymer matrix has a pore size of about 50-500 microns (column 9, lines 54-64).

Regarding claims **22, 48,** Borenstein et al teach tissue engineering construct, wherein artificial organs of the invention have a specific macroscopic shape that can be fashioned to the specific needs of a patient and may be fabricated (prior to cell seeding) into useful articles for tissue engineering and tissue-guided regeneration applications, including reconstructive surgery, Therefore, one of skill in the art would have been sufficiently motivated to make any of the claimed shapes in order to utilize the construct for a specific application.

Regarding claims **5, 34,** it would have been obvious to try said mixture because it would have been well within the ability of the ordinary artisan since Borenstein teaches both of these

compounds, that is poly(lactic acid and poly(lactic acid-co-glycolic acid) (column 11, lines 59-29) .

Regarding claims **7-11, 27-32,** Borenstein teaches the polymer should be selected for biocompatibility at the time of implant and relatively high rigidity is advantageous so that the scaffold can withstand the contractile forces exerted by cells growing within the scaffold (column 7 lines 58-65) Borenstein further teaches that the scaffold contains the same polymers as that of the instant invention. Therefore, any properties of claimed scaffold are inherent in the scaffold. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Regarding claim **47,** Borenstein teaches the mechanical force is compressive stress (example 4).

Borenstein does not specifically teach embryonic stem cell directed differentiation.

However, prior to the time of filing **Xu** (US 7,425,448, filed July 12, 2002; claiming priority to Jul 12, 2001) teaches the differentiation of human ES cells into cardiomyocytes (columns 23-24, example 2).

Regarding claims **2-3, 24-25,** Xu teaches human embryonic stem cells (title).

Regarding claims **44, 49,** Xu teaches it is beneficial to include in the medium one or more cardiotropic factors alone or in combination to enhance proliferation or survival of cardiomyocyte type cells (column 12, lines 44-67, column 13, lines, 1-14).

Regarding claims **71, 73**, Xu teaches the addition of growth factors Activin A and IGF II (column 12, lines 65-67).

Regarding claim **76-79,** Xu teaches the addition of cytokines of the TGF beta family (column 12, lines 55-65, column 13, lines, 1-14).

Regarding claims 43, 50, Xu et al teach the directed differentiation of hES into cardiomyocytes in a serum-free culture medium (column 11, lines 48-65).

Accordingly, it would have been obvious to the skilled artisan to modify the teachings of Borenstein to utilize HES cells as taught by Xu with a reasonable expectation of success. One of ordinary of skill in the art would have been motivated to utilize hES in combination with cardiotropic growth factor in order to direct differentiation of hES cells into cardiomyocytes for constructing a tissue engineering construct, because Xu suggests that hES cell population may be formulated as a medicament for treating a condition of the heart via reconstituting or supplementing contractile activity in cardiac tissue, via differentiated hES cells into cardiomyocytes for treatment of a heart condition in an individual, in which the individual is administered a cell population of this invention in a suitable formulation and one of skill in the art would readily recognize the use of a heart tissue-like engineered construct for treating a condition of the heart via reconstituting or supplementing contractile activity in cardiac tissue, via differentiated hES cells into cardiomyocytes for treatment of a heart condition in an individual, as noted by Xu (abstract). This is underscored by the teachings of Borenstein utilizing embryonal or fetal cells or stem cells for translating two-dimensional microfabrication technology into the third dimension as two-dimensional templates are fabricated using high-resolution molding processes and these templates are then bonded to form three-dimensional scaffold structures with closed lumen so the scaffolds can serve as the template for cell adhesion and growth by cells that are added to the scaffolds through the vessels, holes or pores, wherein these scaffolds can be formed by layering techniques, to interconnect flat template sheets to build up a fully vascularized organ (abstract). This is underscored by the teachings of

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

***Applicants' Arguments***

Applicants argue that they traverse all these rejections. The present application, U.S.S.N. 10/731,672, filed December 9, 2003, claims priority to U.S. Provisional Patent Application Serial No. 60/432,228, filed on December 10, 2002 (the '228 application), and U.S. Provisional Patent Application Serial No. 60/443,926, filed on January 31, 2003 (the '926 application). Applicant submits that Sherwood was available online on September 10, 2002, less than one year prior to the filings of the provisional applications, to which the present application claims priority. Applicant therefore re-submits herewith a Declaration under 37 C.F.R. § 1.131, signed by inventor Shulamit Levenberg, Ph.D., for the purpose of removing Sherwood from consideration by the Examiner. The Declaration and its supporting exhibit were submitted on July 7, 2010, in response to the last office action, and have successfully removed the cited Griffith as acknowledged by the Examiner. As the Griffith reference had an effective date (February 8, 2002) that is prior to the effective date (September 10, 2002) of the Sherwood, the previous submission of the Declaration in fact should have removed both references for consideration. Regardless, Applicant hereby reiterates that the Declaration and the exhibit set out that the conception and reduction to practice of the claimed invention had been made prior to February 8, 2002, and respectfully submits that they clearly also predate the effective date (September 10, 2002) of the cited Sherwood. Therefore, Sherwood should be removed from consideration by the Examiner. To the extent that all the obviousness rejections based on the combination of Sherwood with Buttery and Athanasious 1, even further in view of additional references, may be applicable to the presently pending claims, Applicant respectfully submits that they should be obviated upon submission of this Declaration under 37 C.F.R. § 1.131. Applicant's arguments have been fully considered but are not persuasive.

In response, in the instant the declaration by S. Levenberg discloses the invention which antedates the Sherwood reference, therefore the Sherwood reference has been withdrawn.

***Conclusion***

**No claim is allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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